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EXAMINER

SAOUD, CHRISTINE J

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1647

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/578,856	Applicant(s) VOLLMERS, PHILLIP	
	Examiner Christine J. Saoud	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-43 and 48-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-43 and 48-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/17/08/ 4/16/09, 5/18/09</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 22 April 2009 is acknowledged.

Claims 1-26 have been canceled and claims 27-47 were added in the amendment filed 11 May 2006. In the amendment filed 22 April 2009, claims 44-47 were canceled and claims 27-43 were amended and claims 48-51 were added. Claims 27-43 and 48-51 are currently pending and under examination.

Priority

It is noted that the instant application has been filed as a 371 application of PCT/DE2004/002503. However, the instant application does not appear to obtain benefit to the PCT application because the inventorship is not the same. The inventors on PCT/DE2004/002503 is Heinz Vollmers and Hans Konrad Muller-Hermelink while the inventor of the instant application is Phillip Vollmers.

Applicant is advised that art will be applied accordingly.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

Art Unit: 1647

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The information disclosure statements filed 11/17/08 and 4/16/09 fail to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. Patents and U.S. Patent Application Publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the Examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

It is also noted that several references are in German and a translation of the abstract and/or relevant portions have not been provided. These references have only been considered in so far as the Examiner reads German. If the Applicant would like the abstract or the entirety of the reference to be considered, an English translation will be necessary.

Specification

The disclosure is objected to because of the following informalities:

(a) The description of the Figures found in the Specification at page 19 does not reflect the Figures which were submitted on 11 May 2006. Furthermore, Figure 1 and

Figure 2 have no labels on the axis, therefore, interpretation of the data contained therein is impossible.

b) The specification does not cross-reference the related priority applications. Please note that the priority applications cannot be incorporated by reference after the original filing of the instant application. For additional information on claiming benefit to an earlier filed application see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

c) The specification refers to amino acid sequences without proper reference to a Sequence identifier. At pages 8-9 of the specification, reference is made to portions of the amino acid sequence of SEQ ID NO:1 and 3. However, there is no indication of where within the full-length sequence the portion is located. When reference is made to a subsequence of a larger sequence which is represented by Sequence identifier, reference should be made to the amino acid positions which are being referenced (e.g. amino acids 10-18 of SEQ ID NO:1). The specification should be amended to make reference to the particular portions of SEQ ID NO:1 and 3 where the recited sequences can be found.

Appropriate correction is required.

Claim Objections

Claim 43 is objected to because of the following informalities: the claim refers to amino acid sequences without proper reference to a Sequence identifier because there is no indication of where within the full-length sequence the portion is located. When

Art Unit: 1647

reference is made to a subsequence of a larger sequence which is represented by Sequence identifier, reference should be made to the amino acid positions which are being referenced (e.g. amino acids 10-18 of SEQ ID NO:1). The claim should be amended to make reference to the particular portions of SEQ ID NO:1 and 3 where the recited sequences can be found.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 72-79, 82-88 and 98-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an antibody comprising SEQ ID NO:1 (VL) and SEQ ID NO:3 (VH) and/or binding fragments comprising the VL/VH and which bind to LDL or oxidized LDL, does not reasonably provide enablement for any antibody with binding specificity for the antigen and having: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Art Unit: 1647

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as broadly encompassing of an antibody or antigen binding fragment thereof with binding specificity for LDL or oxidized LDL, and where the antibody has: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3 from SEQ ID NO:1 and/or SEQ ID NO:3.

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure in the Specification

The specification discloses a single isolated antibody, SAM-6 and sometimes called SAM-6.10, which binds LDL and oxidized LDL. At the time of filing, Applicant's specification did not reveal the structural identity of the antigen but generally characterized the antigen as LDL or oxidized LDL and the ability of the antibody to bind these LDL molecules was measured by an ELISA assay (page 14 of the specification).

Art Unit: 1647

The sequence for the antibody (SAM-6 and/or SAM-6.10) is disclosed for VL and VH (SEQ ID NO:1 and 3, respectively). The antibody was shown to reduce LDL levels in vivo (Experiments 1 and 2, although no data is provided since the Figures which are discussed in the Specification are not present in the Application).

The specification contemplates but does not specifically disclose working embodiments for just any of the antibody structures encompassed by the claims much less that any modified antibody would have the required properties of binding LDL or oxidized LDL or complementary carbohydrate structures since no actual structure of the specific antigen is provided.

Without sufficient guidance in the written description alone, the ordinary artisan could not practice making and using the myriad antibody embodiments encompassed by the claims because the specification and claims do not define which regions and domains are subject to variation, which regions or domains could tolerate the introduction of the variation, or the nature and extent of the variation. For example, the claims are not limited to whether the extent of variation comprises amino acid substitutions, insertions, deletions and combinations thereof so that the ordinary artisan could predict which variation would not compromise antigen binding specificity. The claims are not limited as to whether the variation occurs in the antigen binding domains or Fc regions, or the CDRs and/or framework domains. Thus it is not readily apparent from the specification or the original claims as filed, how the ordinary artisan could practice the invention without incurring undue experimentation in order to identify a reasonable number of working embodiments based on the extent of antibody variation

Art Unit: 1647

encompassed by the claims. Further, the claims encompass antibody embodiments having structures that are generally viewed in the field of art as being non-operative or at least unpredictable as to their antigen affinity, namely, antibodies having single variable domains or those having fewer than the full complement of both VL and VH CDRs. Thus the ordinary artisan could not reduce to practice the myriad embodiments and expect to obtain a reasonable number of working embodiments absent undue experimentation at the levels of gene manipulation, antibody screening and bioassay performance.

Prior Art Status: Single CDR-domain Antibodies

The claims encompass isolated antibodies comprising a single CDR domain (and less than the full complement of VH/VL CDRs) from SAM-6 antibody. Applicants have not shown that any isolated any antibody comprising less than a full complement of VH/VL CDRs from a parent SAM-6 antibody of SEQ ID NO:1 and 3 would retain the antigen binding to the LDL and oxidized LDL tested. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework residues influence binding.

MacCallum et al. (J. Mol. Biol. 262:732-745 (1996)) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

de Pascalis *et al.* (Journal of Immunology 169, 3076-3084 (2002)) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (BBRC 307, 198-205, (2003)) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (J. Mol. Biol. 320, 415-428 (2002)) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al.* (Mol. Immunol. 44: 1075-1084 (2007)) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were

Art Unit: 1647

involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. 293, 865-881 (1999)) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. 294, 151-162 (1999)) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH CDRs and VL CDRs).

Analyzing applicants own disclosure, which while it does contemplates divergent CDR residues, the only working example is the SAM-6 antibody having heavy chain CDRs paired with complementary light chain CDRs. Additionally, the data indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no

Art Unit: 1647

examples of mixing or matching of the light chain CDRs or heavy chain CDRs and most importantly there is no working example of placing a single CDR domain of a heavy chain and/or a light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass antibodies comprising VH domains, VL domains and CRDs which vary in the extent to which they resemble the corresponding domain in the parent SAM-6 antibody of SEQ ID NO:1 and 3. This variation can comprise any number and kind of amino acid substitutions. It is not well established in the art that all variable domains are amenable to modifications much less that that substitutions are for conservative amino acids. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al.* (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr

Art Unit: 1647

substitutions at Trp 33 retained “a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding” (Table 1). However, Kobayashi notes “replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv” (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxigenin and ouabain. Histogram analysis of the mutants (Figure 2) reveals that “not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects and demonstrate that any conservative substitution within any CDR cannot be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFv derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, “a very conservative substitution may abolish binding” while “in another, a non-conservative substitution may have very little effect on the binding” (p. 35, Col. 1, ¶1).

Prior Art Status for Single Variable Domain Antibodies

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which

Art Unit: 1647

maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is

Art Unit: 1647

merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(f) he did not himself invent the subject matter sought to be patented.

Claims 27-43 and 48-51 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 1 531 162 A1 (Vollmers et al., May 18, 2005).

Vollmers (Heinz) et al. teach an antibody which is identical to that of SEQ ID NO:1 and 3 of the instant application. Therefore, the reference anticipates the instant claims.

Claims 27-43 and 48-51 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The instant application claims benefit to a PCT application DE2004/002503 for which the Applicant is Heinz Vollmers. The inventor on the instant application is Phillip Vollmers (also spelled Philip on some of the application papers). Therefore, it would appear that the applicant did not invent the claimed subject matter.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647